REMARKS/ARGUMENTS

Applicants acknowledge the withdrawal of claims 47, 49 and 50. The pending claims are 1-3, 14, 16-18, 22-24, 32-35, 48 and 51.

Rejection under 35 U.S.C. § 102(b)

The Examiner has rejected claims 1-3, 14, 16-18, 22-24, 48 and 51 under 35 U.S.C. § 102 (b) as being anticipated by Del Val et al. MPEP 706.02(a)(II)(A) states "If the publication or issue date of the reference is more than 1 year prior to the effective filing date of the application (MPEP § 706.02), the reference qualifies as prior art under 35 U.S.C. 102(b)." Applicants respectfully disagree with the Examiner's rejection because, as discussed below, applicants assert that Del Val et al. reference was not published prior to February 4, 2001. However, in order to facilitate prosecution in this case applicants have amended the pending claims, without prejudice or disclaimer, to recite the SEQ ID NOs of the peptides disclosed in the provisional application to which the present application claims priority. Thus, the pending claims are entitled to a priority date of February 5, 2001, which means that the Del Val et al. reference is not available as 102(b) prior art. Therefore applicants respectfully request that the Examiner withdraw the rejection of claims 1-3, 14, 16-18, 22-24, 48 and 51 under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 102(a)

The Examiner has rejected claims 1-3, 14, 16-18, 22-24, 48 and 51 as being anticipated by Del Val et al. under 35 U.S.C. § 102(a).

Applicants respectfully traverse on three grounds: (i) the Del Val et al. reference is a publication of the inventors and therefore cannot qualify under 102(a) as described in a publication before the invention by the inventors because the inventors could not have published their invention before having invented it; (ii) the Del Val et al. reference is not available under 102(a) because it published after the priority date of the present claims; and (iii) the Del Val et al. reference is not

available as a 102(a) reference because the inventors invented the presently claimed invention prior to its publication.

(i) *Del Val is a publication of the inventors*

First, as discussed in the previous response, the Del Val et al. reference is a publication of the inventors. The Examiner pointed out in the final Office Action that the previously submitted 1.132 declaration was insufficient because it did not describe the role of Suzanne Teuber, who was an author of the publication but not an inventor of the application. Applicants would like to apologize for this omission and address this point here.

In order for a printed publication to anticipate under 35 U.S.C. § 102(a), the publication must describe the work of *another* before the Applicant's invention. See 35 U.S.C. 102(a). In particular, MPEP 2132.01 states "[a]n Applicant's disclosure of his or her own work within the year before the application filing date cannot be used against him or her under 35 U.S.C. § 102(a)". Accordingly, Applicants enclose a second declaration of Dr. Bob Buchanan, the senior author of the Del Val reference and an inventor of the instant application. Dr. Buchanan declares that a co-author of the Del Val reference, Suzanne Teuber, who was not named as an inventor in the instant application, did not make any original contribution to the work described in the Del Val abstract as related to the claims in the instant application. Thus, the Del Val reference describes the inventive work of only the inventors listed in the instant application. For this reason, the Del Val reference does not qualify as prior art under 102(a) to anticipate any of the claims of the instant application because it does not disclose the work of *another*. Accordingly, Applicants respectfully request that this ground for rejection be withdrawn.

(ii) *Del Val published after the priority date of the present claims*

MPEP 706.02(a) states "The examiner must determine the issue or publication date of the reference so that a proper comparison between the application and reference dates can be made. A magazine is effective as a printed publication under 35 U.S.C. 102(b) as of the date it reached the addressee and not the date it was placed in the mail." MPEP 2128 states "A reference is proven to

be a "printed publication" upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it."

Applicants respectfully submit that the Del Val et al. reference was not publicly available prior to the February 5, 2001 filing date of the provisional patent application to which the present claims are entitled to claim priority. The Examiner suggested that either one of two things could be provided to establish when the abstract book was publicly available: "...provide a letter from the publisher of the abstract book indicating when the abstract was first made publicly available, or a declaration by Applicant, since they received the Abstract book, as to when they first received it."

The Applicant does not have a record as to the exact date of receipt of the abstract book. Applicants contacted the publisher to determine the date of shipping of this abstract book, but the publisher did not have record of this as it was over three years ago. However, the publisher did state that their policy is to ship all copies of a particular issue on one day, and that all copies of this issue would have been shipped from within the United States. Applicants enclose a declaration from Swathi Rao stating the aforementioned policy of the publisher, Elsevier.

As evidence of the date of accessibility of the cited reference, Applicants enclose date stamped copies of the abstract book from the Stanford, UC Berkeley, and UC Davis libraries. Stanford Library received the abstract book on February 21st, 2001. UC Berkeley Library received it on March 6th, 2001, and UC Davis received it on March 16th, 2001. Applicants contend that since all publicly available copies of the abstract book were shipped from the publisher on one day, the earliest stamped date of receipt, February 21st, 2001 at Stanford Library, is the earliest date of public availability. This date is still more than two weeks later than the Applicant's February 5th, 2001 priority date. Thus, the Del Val reference does not qualify as 102(a) prior art to anticipate any of the claims of the instant application. Applicants therefore respectfully request this ground for rejection be withdrawn.

(iii) *The inventors invented the present claims prior to the publication of Del Val*

Even if the Del Val et al. reference was publicly available as of February 1, 2001, it is still not available as 102(a) prior art as it was not "described in a printed publication in this or a foreign country, before invention thereof by the applicant for patent." Provided herewith are three declarations, one from each of the inventors, asserting that they invented the presently claimed invention prior to February 1, 2001. As evidence thereof, each has submitted a draft paper describing the present invention prepared prior to February 1, 2001.

Therefore applicants respectfully request that the Examiner withdraw the rejection of claims 1-3, 14, 16-18, 22-24, 48 and 51 based upon 35 U.S.C. § 102(a)

Rejection under 35 U.S.C. § 103(a)

As a preliminary matter, Applicants thank the Examiner for once again advising, in Section 6 of the Office Action, the Applicants of their obligation under 37 C.F.R. § 1.56 to point out any instances of lack of common ownership with respect to co-pending applications in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 § U.S.C. 102(e), (f), or (g) prior art under 35 U.S.C. § 103(a). Applicants again wish to state that all co-pending applications are commonly owned.

The Examiner has rejected claims 32-35 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Del Val et al., in view of U.S. Patent No. 4,281,061. Applicants respectfully traverse this rejection.

35 U.S.C. § 103(a) states: "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." As shown above, the Del Val reference does not qualify as 102(b) prior art or as 102(a) prior art, and is therefore not available for use in a 103(a) rejection. Applicants therefore respectfully request that this ground for rejection be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 416272000200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: February 23, 2006

Respectfully submitted,

By _____

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Registration No.: 48,751
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BRIEF SUMMARY

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FLOVENT® 44 mcg
(fluticasone propionate, 44 mcg)
Inhalation Aerosol

FLOVENT® 110 mcg
(fluticasone propionate, 110 mcg)
Inhalation Aerosol

FLOVENT® 220 mcg
(fluticasone propionate, 220 mcg)
Inhalation Aerosol

For Oral Inhalation Only

The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS: FLOVENT Inhalation Aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. [illegible]

WARNINGS: [illegible]

PRECAUTIONS: [illegible]

[illegible]

ADVERSE REACTIONS: [illegible]

Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in US Controlled Clinical Trials With MDI in Patients Previously Receiving Bronchodilators and/or Inhaled Corticosteroids

Adverse Event	Placebo (n = [illegible]) %	FLOVENT 88 mcg twice daily (n = [illegible]) %	FLOVENT 220 mcg twice daily (n = [illegible]) %	FLOVENT 440 mcg twice daily (n = [illegible]) %
Ear, nose, and throat				
Pharyngitis	7	10	14	14
Nasal congestion	8	8	16	10
Sinusitis	4	3	6	5
Nasal discharge	3	5	4	4
Dysphonia	1	4	3	6
Allergic rhinitis	4	5	3	3
Oral candidiasis	1	2	3	5
Respiratory				
Upper respiratory infection	12	16	22	16
Influenza	2	3	8	5
Neurological				
Headache	14	17	22	17
Average duration of exposure (days)	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

OVERDOSAGE: [illegible]

GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent No. 4,335,121 April 1999
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1036 A Comparison of Cutaneous, Conjunctival and Bronchial Reactivity to P Pratense

Gideon Lack, Graham Roberts, Caitriona Hurley St Mary's Hospital, London, UK

OBJECTIVE: To determine whether there is a relationship between cutaneous, conjunctival and bronchial sensitivities to Phleum pratense (timothy grass) in individual children and teenagers with seasonal allergic asthma and rhinitis.

METHODS: 39 subjects (27 boys) aged 3 to 16 (average 11.9) years were assessed in this study. Specific IgE (Pharmacia Cap) to P pratense were assayed in all subjects. Skin prick testing was performed in 38 subjects with half-log. increasing concentrations of P pratense (ALK); the concentration giving a 3mm weal was determined by interpolation. Conjunctival testing was performed in all subjects using half-log. increasing concentrations of P pratense; the concentration giving a score of 5 on a standardised, validated scoring system recorded by one observer was determined by interpolation. Bronchial challenges with P pratense was performed in 25 subjects with half-log. increasing concentrations delivered by a Pacijet nebuliser and lung function measured by Masterscreen spirometer (Jaeger); the PC20 was calculated. A comparison between the factors was made using correlation coefficients; the Bonferroni transformation was used to account for the multiple comparisons. Calculations were performed using Stata 6.

RESULTS: A significant correlation was found between specific IgE to P pratense and cutaneous sensitivity. However, no other significant relationships were found between specific IgE levels, cutaneous reactivity, conjunctival sensitivity or bronchial reactivity.

CONCLUSIONS: The data presented demonstrate that the sensitivities of different organs to P pratense are independent of each other. This agrees with the different patterns of clinical symptoms seen in children with grass pollen allergy.

Comparison between specific IgE and end-organ sensitivities

	Specific IgE	Cutaneous	Conjunctival	Bronchial
Specific IgE	-	-	-	-
Cutaneous	-0.568 (p=0.03)*	-	-	-
Conjunctival	-0.251 (p=1)	0.285 (p=0.40)	-	-
Bronchial	-0.403 (p=1)	0.208 (p=1)	0.138 (p=1)	-

*Cutaneous sensitivity and specific IgE both logarithmically transformed. P values modified using the Bonferroni transformation to take into account the multiple comparisons.

1037 Comparison of the Molecular and Immunological Properties of Natural and Recombinant Art V 1, the Major Allergen of Artemisia Vulgaris Pollen

Martin Himly, Renate Steiner§, Ronald Van Ree¶, Christof Ebner§, Fatima Ferreira** *University of Salzburg, Salzburg, Austria §University of Vienna, Vienna, Austria ¶Central Laboratory of the Netherlands Blood Transfusion Service, Amsterdam, Netherlands

Pollen of mugwort (Artemisia vulgaris) represent one of the main causes for type I allergy in late summer and fall in Europe. Mugwort, a member of the Asteraceae or Compositae plant family, pollinates by wind and is widely distributed throughout the temperate climate regions of Central Europe. The major allergen of mugwort pollen has been determined by immunoblots with a large collection of sera from mugwort pollen-sensitized patients. This protein, which is recognized by 95 % of mugwort-allergic patients, was designated Art v 1. When subjected to SDS-PAGE it appears as a heterogeneous band in the MW range of 24 to 28 kDa. Recombinant Art v 1, in contrast, migrates at approximately 17 to 18 kDa, although the theoretical MW derived from the polypeptide chain is 10.8 kDa. Both natural and recombinant Art v 1 have been purified to homogeneity. In this study we report the molecular and immunological properties of purified recombinant Art v 1 in comparison to its natural counterpart. Natural Art v 1 was found to contain carbohydrate as demonstrated by positive PAS-staining. Mass measurements by Matrix-assisted laser desorption ionization-mass spectrometry (MALDI-MS) were performed. By these means the molecular mass of purified recombinant Art v 1 was determined to be 10800, whereas in the case of purified natural Art v 1 two rather broad mass peaks with maxima at about 13400 and 15600 were detected. These differences in MW were assigned to the sugar content, which also turned out to protect the polypeptide chain from proteolytic digest. Binding experiments with plant lectins were performed in order to characterize the carbohydrate moieties. However, no common type of N-linked glycosylation could be detected. ELISA experiments with a panel of patients' sera revealed two distinct binding patterns of IgE antibodies: one class of sera reacted similarly with natural and recombinant Art v 1, whereas the other class showed extremely weak or no reactivity to recombinant in comparison to the natural allergen. In inhibition ELISA experiments, natural Art v 1 totally abolished the interaction of IgE with its recombinant counterpart, whereas recombinant Art v 1 gave only 50 % inhibition of IgE-binding to the natural allergen. Purified natural and recombinant Art v 1 were also subjected to periodate treatment and reduction/alkylation procedures. By subsequently performed immunoblotting and ELISA inhibition experiments with patients' sera more conclusions on the nature of the present IgE epitopes of natural and recombinant Art v 1 could be drawn. Taken together the results of this study show a high impact of glycosylation on the allergenicity of the major mugwort pollen allergen Art v 1.

1038 A Major New Allergen From Ragweed Pollen

Greg Del Val, Joshua H Wong*, Suzanne Teuber§, Oscar L Frick¶, Bob B Buchanan** *UC Berkeley, Berkeley, CA §UC Davis, Davis, CA ¶UC San Francisco, San Francisco, CA

Ragweed pollen has a lipid layer on the surface, which has been extracted and routinely discarded for more than 50 years in order to produce allergy test preparations. The symptoms in pollen allergy, that appear after a few minutes, are believed to be due to allergens located on the pollen surface, which includes the lipid layer. As it has been demonstrated with defatted ragweed pollen (Marsh DG et al JACI 1981, 67: 206-222), there are important extracellular allergens released in a short time period- e.g. Amb a 5 in 16 minutes, versus the major allergens described, Amb a 1 and 2, in 12-24 hours. However, these authors and others have not reported significant differences in the first-released allergens from the complete and defatted preparations. In our work, we show a difference in the population of the first-released allergens from complete and defatted pollen. We have identified and characterized an allergen located in the lipid fraction that is discarded during the defatting process. The allergen, which appears to be a major pollen glycoprotein, has a molecular mass of 30 kDa and contains at least one disulfide bond. Amino acid sequencing data indicate that the protein has not been previously described from pollen or other sources. Finally, after performing IgE-immunoblots with 25 sera of ragweed-sensitive patients, we have found that the 30 kDa protein is recognized by all of them, thus qualifying it as a major allergen that is perhaps missed in current screens. Furthermore, our results are reinforced by the fact that dogs sensitized to ragweed also uniformly recognize the allergen. These findings suggest that the lipid fraction containing the 30 kDa allergen and possibly others should be included in allergy testing and immunotherapy regimes.

1039 Seasonal Variation in the Indoor Mold Aerospora Among Inner-city Homes

H James Wedner, Anupma Dixit, Roosevelt Peabody Washington University School of Medicine, St Louis, MO

INTRODUCTION: Sensitization to the indoor mold aerospora may play a significant role in the increasing prevalence of asthma among inner-city dwelling children and adults. To evaluate indoor mold contamination, we have used volumetric spore sampling for both total and viable spores in 40 homes in the East St. Louis, IL (ESL) area.

METHODS: At least one asthmatic patient (usually 2 or more) resided in each of the homes selected. Sampling was carried out throughout the year using a Burkard Personal Volumetric spore trap and viable spore trap. Viable spores were collected onto MEA plates. The kitchen, TV room and

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BRIEF SUMMARY

FLOVENT™ 44 mcg
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Inhalation Aerosol

FLOVENT™ 110 mcg
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Inhalation Aerosol

FLOVENT™ 220 mcg
(fluticasone propionate, 220 mcg)
Inhalation Aerosol

For Oral Inhalation Only

The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS: FLOVENT Inhalation Aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use.

WARNINGS:

Particular care is needed for patients who are transferred from systemically active corticosteroids to FLOVENT Inhalation Aerosol because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although fluticasone propionate inhalation aerosol may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to fluticasone propionate inhalation aerosol. In a trial of 96 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive reduction of prednisone dose was allowed only when lung function, symptoms, and as-needed beta-agonist use were better than or comparable to that seen before initiation of prednisone dose reduction. Lung function (forced expiratory volume in 1 second [FEV_1] or morning peak expiratory flow rate [AM PEFR]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to fluticasone propionate inhalation aerosol may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, and arthritis.

Persons who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Fluticasone propionate inhalation aerosol is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT Inhalation Aerosol, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with FLOVENT Inhalation Aerosol should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physicians immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with fluticasone propionate inhalation aerosol. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS:

General: During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of fluticasone propionate inhalation aerosol in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with fluticasone propionate inhalation aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing fluticasone propionate inhalation aerosol.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, fluticasone propionate inhalation aerosol should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if an adolescent's growth appears slowed.

The long-term effects of fluticasone propionate in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received fluticasone propionate inhalation aerosol on a continuous basis for periods of 3 years or longer. In clinical studies with patients treated for nearly 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including fluticasone propionate.

In clinical studies with inhaled fluticasone propionate, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with fluticasone propionate inhalation aerosol, but at times therapy with fluticasone propionate may need to be interrupted.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS).

Information for Patients: Patients being treated with FLOVENT Inhalation Aerosol should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should use FLOVENT Inhalation Aerosol at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first day or two of treatment; however, the full benefit may not be achieved until treatment has been administered for 1 to 2 weeks or longer. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.

For the proper use of FLOVENT Inhalation Aerosol and to attain maximum improvement, the patient should read and follow carefully the accompanying Patient's Instructions for Use.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone propionate demonstrated no tumorigenic potential in studies of oral doses up to 1000 mcg/kg (approximately 2 times the maximum human daily inhalation dose based on mcg/m^2) for 78 weeks in the mouse or inhalation of up to 57 mcg/kg (approximately 1/4 the maximum human daily inhalation dose based on mcg/m^2) for 104 weeks in the rat.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test when administered at high doses by the oral or subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

No evidence of impairment of fertility was observed in reproductive studies conducted in rats dosed subcutaneously with doses up to 50 mcg/kg (approximately 1/4 the maximum human daily inhalation dose based on mcg/m^2) in males and females. However, prostate weight was significantly reduced in rats.

Pregnancy: *Teratogenic Effects*: Pregnancy Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (approximately 1/10 and 1/2 the maximum human daily inhalation dose based on mcg/m^2, respectively), revealed fetal toxicity characteristic of potent glucocorticoid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed following subcutaneous doses of 4 mcg/kg (approximately 1/25 the maximum human daily inhalation dose based on mcg/m^2). However, following oral administration of up to 300 mcg/kg (approximately 3 times the maximum human daily inhalation dose based on mcg/m^2) of fluticasone propionate to the rabbit, there were no maternal effects nor increased incidence of external, visceral, or skeletal fetal defects. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY section of full prescribing information).

Less than 0.008% of the administered dose crossed the placenta following oral administration of 100 mcg/kg to rats or 300 mcg/kg to rabbits (approximately 1/2 and 3 times the maximum human daily inhalation dose based on mcg/m^2, respectively).

There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral glucocorticoids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from glucocorticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous glucocorticoid dose and many will not need glucocorticoid treatment during pregnancy.

Nursing Mothers: It is not known whether fluticasone propionate is excreted in human breast milk. Subcutaneous administration of 10 mcg/kg tritiated drug to lactating rats (approximately 1/20 the maximum human daily inhalation dose based on mcg/m^2) resulted in measurable radioactivity in both plasma and milk. Because glucocorticoids are excreted in human milk, caution should be exercised when fluticasone propionate inhalation aerosol is administered to a nursing woman.

Pediatric Use: One hundred thirty-seven (137) patients between the ages of 12 and 16 years were treated with fluticasone propionate inhalation aerosol in the US pivotal clinical trials. The safety and effectiveness of FLOVENT Inhalation Aerosol in children below 12 years of age have not been established. Oral corticosteroids have been shown to cause a reduction in growth velocity in children and teenagers with extended use. If a child or teenager on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see PRECAUTIONS).

Geriatric Use: Five hundred seventy-four (574) patients 65 years of age or older have been treated with fluticasone propionate inhalation aerosol in US and non-US clinical trials. There were no differences in adverse reactions compared to those reported by younger patients.

ADVERSE REACTIONS: The following incidence of common adverse experiences is based upon 7 placebo-controlled US clinical trials in which 1243 patients (509 female and 734 male adolescents and adults previously treated with as-needed bronchodilators and/or inhaled corticosteroids) were treated with fluticasone propionate inhalation aerosol (doses of 88 to 440 mcg twice daily for up to 12 weeks) or placebo.

Overall Adverse Experiences With >3% Incidence on Fluticasone Propionate in US Controlled Clinical Trials With MDI in Patients Previously Receiving Bronchodilators and/or Inhaled Corticosteroids

Adverse Event	Placebo (n = 475) %	FLOVENT 88 mcg twice daily (n = 488) %	FLOVENT 220 mcg twice daily (n = 95) %	FLOVENT 440 mcg twice daily (n = 185) %
Ear, nose, and throat				
Pharyngitis	7	10	14	14
Nasal congestion	8	8	16	10
Sinusitis	4	3	6	5
Nasal discharge	3	5	4	4
Dysphonia	1	4	3	8
Allergic rhinitis	4	5	3	5
Oral candidiasis	1	2	3	5
Respiratory				
Upper respiratory infection	12	15	22	16
Influenza	2	3	8	5
Neurological				
Headache	14	17	22	17
Average duration of exposure (days)	44	66	64	59

The table above includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in the combined fluticasone propionate inhalation aerosol groups and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account.

These adverse reactions were mostly mild to moderate in severity, with ≤2% of patients discontinuing the studies because of adverse events. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria and rash and other rare events of angioedema and bronchospasm, have been reported.

Systemic glucocorticoid side effects were not reported during controlled clinical trials with fluticasone propionate inhalation aerosol. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, e.g., Cushing's syndrome, could occur.

Other adverse events that occurred in these clinical trials using fluticasone propionate inhalation aerosol with an incidence of 1% to 3% and which occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Pain in nasal sinus(es), rhinitis.
Eye: Irritation of the eye(s).
Gastrointestinal: Nausea and vomiting, diarrhea, dyspepsia and stomach disorder.
Miscellaneous: Fever.
Mouth and Teeth: Dental problem.
Musculoskeletal: Pain in joint, sprain/strain, aches and pains, pain in limb.
Neurological: Dizziness/giddiness.
Respiratory: Bronchitis, chest congestion.
Skin: Dermatitis, rash/skin eruption.
Urogenital: Dysmenorrhea.

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In a 16-week study in patients with asthma requiring oral corticosteroids, the effects of fluticasone propionate inhalation aerosol, 660 mcg twice daily (n = 32) and 880 mcg twice daily (n = 32), were compared with placebo. Adverse events (whether considered drug-related [illegible] by the investigator) reported by more than 3 patients in either fluticasone propionate group [illegible] propionate than placebo are shown below.

Ear, Nose, and Throat: Pharyngitis (9% and 25%), nasal congestion (19% and 22%), sinusitis (19% and 22%), nasal discharge (16% and 16%), dysphonia (19% and 9%), pain in nasal sinus(es) (13% and 0%), Candida-like oral lesions (16% and 9%), oropharyngeal candidiasis (25% and 19%).

Respiratory: Upper respiratory infection (31% and 19%), influenza (0% and 13%).

Other: Headache (28% and 34%), pain in joint (19% and 13%), nausea and vomiting (22% and 16%), muscular soreness (22% and 13%), malaise/fatigue (22% and 28%), insomnia (3% and 13%).

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of fluticasone propionate in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, causal connection to fluticasone propionate, or a combination of these factors.

Ear, Nose, and Throat: Throat soreness and irritation, hoarseness, laryngitis, aphonia.
Endocrine and Metabolic: Cushingoid features, growth velocity reduction in children/adolescents, weight gain, hyperglycemia.
Psychiatry: Restlessness, agitation, aggression, depression.
Respiratory: Immediate bronchospasm, asthma exacerbation, dyspnea, wheeze, chest tightness, bronchospasm, cough.
Skin: Pruritus, contusions, ecchymoses.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS: Eosinophilic Conditions).

OVERDOSAGE: Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS). Inhalation by healthy volunteers of a single dose of 1760 or 3520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of 1320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. The oral and subcutaneous median lethal doses in rats and mice were >1000 mg/kg (>2000 times the maximum human daily inhalation dose based on mg/m^2).

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

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1036 A Comparison of Cutaneous, Conjunctival and Bronchial Reactivity to P Pratense

Gideon Lack, Graham Roberts, Caitriona Hurley St Mary's Hospital, London, UK

OBJECTIVE: To determine whether there is a relationship between cutaneous, conjunctival and bronchial sensitivities to Phleum pratense (timothy grass) in individual children and teenagers with seasonal allergic asthma and rhinitis.

METHODS: 39 subjects (27 boys) aged 3 to 16 (average 11.9) years were assessed in this study. Specific IgE (Pharmacia Cap) to P pratense were assayed in all subjects. Skin prick testing was performed in 38 subjects with half-log. increasing concentrations of P pratense (ALK); the concentration giving a 3mm weal was determined by interpolation. Conjunctival testing was performed in all subjects using half-log. increasing concentrations of P pratense; the concentration giving a score of 5 on a standardised, validated scoring system recorded by one observer was determined by interpolation. Bronchial challenges with P pratense was performed in 25 subjects with half-log. increasing concentrations delivered by a Parijet nebuliser and lung function measured by Masterscreen spirometer (Jaeger); the PC20 was calculated. A comparison between the factors was made using correlation coefficients; the Bonferroni transformation was used to account for the multiple comparisons. Calculations were performed using Stata 6.

RESULTS: A significant correlation was found between specific IgE to P pratense and cutaneous sensitivity. However, no other significant relationships were found between specific IgE levels, cutaneous reactivity, conjunctival sensitivity or bronchial reactivity.

CONCLUSIONS: The data presented demonstrate that the sensitivities of different organs to P pratense are independent of each other. This agrees with the different patterns of clinical symptoms seen in children with grass pollen allergy.

Comparison between specific IgE and end-organ sensitivities

	Specific IgE	Cutaneous	Conjunctival	Bronchial
Specific IgE	-	-	-	-
Cutaneous	-0.568 (p=0.03)*	-	-	-
Conjunctival	-0.251 (p=1)	0.285 (p=0.40)	-	-
Bronchial	-0.403 (p=1)	0.208 (p=1)	0.138 (p=1)	-

*Cutaneous sensitivity and specific IgE both logarithmically transformed. P values modified using the Bonferroni transformation to take into account the multiple comparisons.

1037 Comparison of the Molecular and Immunological Properties of Natural and Recombinant Art V 1, the Major Allergen of Artemisia Vulgaris Pollen

Martin Himly, Renate Steiner§, Ronald Van Ree¥, Christof Ebner§, Fatima Ferreira** *University of Salzburg, Salzburg, Austria §University of Vienna, Vienna, Austria ¥Central Laboratory of the Netherlands Blood Transfusion Service, Amsterdam, Netherlands

Pollen of mugwort (Artemisia vulgaris) represent one of the main causes for type I allergy in late summer and fall in Europe. Mugwort, a member of the Asteraceae or Compositae plant family, pollinates by wind and is widely distributed throughout the temperate climate regions of Central Europe. The major allergen of mugwort pollen has been determined by immunoblots with a large collection of sera from mugwort pollen-sensitized patients. This protein, which is recognized by 95 % of mugwort-allergic patients, was designated Art v 1. When subjected to SDS-PAGE it appears as a heterogeneous band in the MW range of 24 to 28 kDa. Recombinant Art v 1, in contrast, migrates at approximately 17 to 18 kDa, although the theoretical MW derived from the polypetide chain is 10.8 kDa. Both natural and recombinant Art v 1 have been purified to homogeneity. In this study we report the molecular and immunological properties of purified recombinant Art v 1 in comparison to its natural counterpart. Natural Art v 1 was found to contain carbohydrate as demonstrated by positive PAS-staining. Mass measurements by Maldi-assisted laser desorption ionization-mass spectrometry (MALDI-MS) were performed. By these means the molecular mass of purified recombinant Art v 1 was determined to be 10800, whereas in the case of purified natural Art v 1 two rather broad mass peaks with maxima at about 13400 and 15600 were detected. These differences in MW were assigned to the sugar content, which also turned out to protect the polypeptide chain from proteolytic digest. Binding experiments with plant lectins were performed in order to characterize the carbohydrate moieties. However, no common type of N-linked glycosylation could be detected. ELISA experiments with a panel of patients' sera revealed two distinct binding patterns of IgE antibodies: one class of sera reacted similarly with natural and recombinant Art v 1, whereas the other class showed extremely weak or no reactivity to recombinant in comparison to the natural allergen. In inhibition ELISA experiments, natural Art v 1 totally abolished the interaction of IgE with its recombinant counterpart, whereas recombinant Art v 1 gave only 50 % inhibition of IgE-binding to the natural allergen. Purified natural and recombinant Art v 1 were also subjected to periodate treatment and reduction/alkylation procedures. By subsequently performed immunoblotting and ELISA inhibition experiments with patients' sera more conclusions on the nature of the present IgE epitopes of natural and recombinant Art v 1 could be drawn. Taken together the results of this study show a high impact of glycosylation on the allergenicity of the major mugwort pollen allergen Art v 1.

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Greg Del Val, Joshua H Wong*, Suzanne Teuber§, Oscar L Frick¥, Bob B Buchanan** *UC Berkeley, Berkeley, CA §UC Davis, Davis, CA ¥UC San Francisco, San Francisco, CA

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H James Wedner, Anupma Dixit, Roosevelt Peabody Washington University School of Medicine, St Louis, MO

INTRODUCTION: Sensitization to the indoor mold aerospora may play a significant role in the increasing prevalence of asthma among inner-city dwelling children and adults. To evaluate indoor mold contamination, we have used volumetric spore sampling for both total and viable spores in 40 homes in the East St. Louis, IL (ESL) area.

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